19. CONSANGUINITY

THE CONSANGUINITY CODINGS

In none of the hospitals visited had any information on consanguinity previously been recorded on the case-sheets of the patients. When discussing what information could be elicited accurately for the purposes of the study the physicians in several of the hospitals felt that the full coding proposed was too elaborate. Accordingly in these centres some simpler system was agreed, that most frequently adopted being: (1) no consanguinity, (2) first cousins, and (3) less closely related than first cousins. The codings adopted for each centre are set out in the appropriate Table IX in the Basic Tabulations by Centres booklet. It is, however, possible to regroup the data where necessary from all centres into the simple three classes mentioned above.

RELIABILITY OF THE DATA

Cross-checks on accuracy of recording could not be arranged and there are, judging from past experience, likely to be some inaccuracies in the data. In particular there may be underrecording resulting from unwillingness of mothers to admit to what is thought, in greater or lesser degree, to be undesirable in many communities.

There is no reason to believe that there were any systematic biasses in recording. The possibility of such errors arising were discussed with those in the hospitals visited and in particular, whenever possible, it was arranged that the mother should be questioned before the child was born. The possible association of consanguinity with conservatism about marrying relatives in the lowest income groups in rapidly developing societies where inbreeding is decreasing raises problems, if there should also be a higher frequency of certain malformations in the lowest income groups. This is mentioned later as a possible contribution to some of the association of consanguinity with anencephalus in Alexandria.

Data from Belfast and Mexico 2 are not included in the main tabulations in this section. In both cases, after consultation with the organizers it was agreed that the data were not complete. As will be seen from Table 19.4, in the 22 centres there were in all 14 000 mothers recorded as related to their husbands in 369 472 marriages for which records of consanguinity were made, i.e., in 3.7% of all marriages. However, the frequency of consanguinity varied very considerably from about 33% in Alexandria to less than 0.1% in Zagreb.

ASSOCIATION OF CONSANGUINITY WITH STILLBIRTHS AND DEATHS OF INFANTS BEFORE LEAVING HOSPITAL

As consanguinity might be expected to be associated with stillbirths and early deaths and with increased malformation frequency it seemed advisable to ensure that any effect of consanguinity on mortality did not merely reflect higher mortality in malformed infants. In Table 19.1, therefore, the frequency of consanguinity is shown in single-born infants who failed to survive, *excluding* those who were malformed.

It will be seen that over-all the mortality in the offspring of consanguineous parents (855/13 736, or 62.1 per 1000 total births) was considerably higher than in those of unrelated parents (12 779/355 710, or 35.9 per 1000). Table 19.2, part A, sets out the data in convenient form for comparison of the effects of consanguinity and mortality in individual centres. Such comparisons were made both using exact χ^2 tests and by calculating an expected number of LBD and SB infants in the offspring of related parents based on the experience of the unrelated parents. As the populations of births are relatively large and the numbers of stillbirths and hospital deaths small, it seems appropriate where possible to use the latter method as the more valid, to treat the ratios as Poisson variables and to test for significance of the differences on that assumption. By reason of the nature of the data a 1% level of significance seems to be appropriate in order to have confidence in the validity of differences. On such a basis the observed numbers of LBDs and SBs in the offspring were higher where the parents were related than where they were not in Bombay, Kuala Lumpur and Singapore. In Czechoslovakia, Hong Kong and Zagreb, where no deaths were observed in the offspring of related parents, comparisons could be made only by exact χ^2 tests. The difference was significant at a 5% level in Hong Kong.

As will be seen, there is considerable variation between centres in the ratio of observed to expected and it is less than unity in a number of centres so that if an expressed inbreeding " load " was calculated (Morton, Crow & Muller, 1956) it would be negative, a phenomenon pointed out by Neel (1963).

Nevertheless, that consanguinity is the main determinant of the observed excess mortality in the offspring of related parents is strongly suggested by the summed data. The frequency in the offspring of marriages of those related as first cousins or closer was 692/10 492 while that in those of less closely related parents was 163/3271; this difference is highly significant ($\chi^2 = 11.38$; DF = 1; $P < 0.001$).

It is of interest to note that in Alexandria, where the consanguinity rates are very high and the mortality also very high and presumably largely socially determined, mortality is the same in the offspring of related and unrelated parents.

MORTALITY BY SEX IN THE FOUR TYPES OF FIRST-COUSIN MARRIAGE

In some of the centres the recording of the types of consanguinity was in some detail and included the four types of first-cousin marriage. The coding used was type A, marriage of the son and daughter of two brothers; type B, marriage of the son and daughter of two sisters; type C, where a sister's daughter marries her brother's son, and type D, where a sister's son marries her brother's daughter. In types A and C there is no possibility of a female infant receiving the same X-chromosome from one of her common grandparents. In types B and D there is a possibility of her receiving such a chromosome or at least one carrying much of the genetic material of one derived from a common grandparent. In type B the probability is 3/16 and in type D 1/8.

If there were sex-linked lethals on a chromosome they could not (by definition) be transmitted by males, but sex-linked subvitals or partially sex-linked lethals (if such exist) could be transmitted and could contribute to a higher mortality in females whose parents were related as in B and D than in those whose parents were related as in A and C. The data from São Paulo, Bombay, Kuala Lumpur, Singapore and Pretoria are suitable for such an analysis and the data are set out in Table 19.3. As will be seen there is no significant difference at a 5% level: 75/1280 (5.8%) and 114/1513 (7.8%) ($\chi^2 = 2.81$, DF = 1; $P < 0.1$). This finding is in agreement with those of Schull (1958).

POSSIBLE FURTHER ANALYSES OF CONSANGUINITY AND MORTALITY DATA

In recent years elaborate approaches to analysis of such consanguinity data have been developed (see Morton, Crow & Muller, 1956; Crow, 1958) and there has recently been a comprehensive review by Schull & Neel (1965). Use of such analyses, however, requires a confident identification of the degree of each consanguineous marriage and use of appropriate coefficients of inbreeding to enable the detriment to the offspring to be expressed in terms of lethal equivalents. The data on which such calculations could be based are set out fully in the Basic Tabulations by Centres booklet. The authors may set out such an analysis later when a number of further inquiries to centres have been answered and they are satisfied that the data are sufficiently accurate to justify more sophisticated numerical treatment.

ASSOCIATION OF CONSANGUINITY AND MALFORMATIONS

Consanguinity and all malformations

When all major malformations are considered it will be seen from Tables 19.2, part B, and 19.4 that a higher proportion of the parents of malformed children than of normal infants were consanguineous and that there is a considerable variation in contribution to the total proportions from different centres. Of the 237 malformed infants born to related parents, the major contributors are Alexandria (48 cases), Bombay (52 cases), Singapore (25 cases), Bogotá (14 cases), Medellín (21 cases), Panama (13 cases) and Pretoria (11 cases). These are all centres where the parental consanguinity rate for all births is high. In contrast, six centres, all with low over-all consanguinity rates, contributed none or a single case. Over-all, there is no material difference in the malformation frequency in the offspring of FC & CFC and LFC parents (Table 19.4) although in both Alexandria and Bombay the frequencies are significantly higher in the offspring of the former than of the latter.

Table 19.2, part B, sets out the data for comparison in the same form as in 19.2, part A, for mortality. The numbers of malformations are relatively small and again the comparisons are made either on the assumption that the ratios may be treated as Poisson variables or by exact χ^2 tests. There appear to be significantly higher malformation frequencies in children born to related parents in Medellín, Cze-

choslovakia, Alexandria, Bombay and Panama. In all the other centres the ratio of observed to expected is greater than unity with the notable exception of Johannesburg, where there is a relative excess of malformed in the offspring of unrelated parents which, on a basis of exact probability, is unlikely to have occurred by chance.

Consanguinity and specific groups of malformations

Little can be learned from consideration of the numbers of related parents of all malformed. These defects are very heterogeneous in etiology and, as has been shown in section 15, a number of them are really the expression of homozygosity for a single-gene mutation.

It is therefore necessary to look at the associations of consanguinity with specific groups of malformations. It would be preferable, of course, to look at those of individual malformations, but in very few are the numbers sufficiently large to permit of meaningful comparisons. The percentage of consanguineous parents of all infants who were not malformed was 3.7%. As may be seen from Table 19.5, this proportion is exceeded in the B, G, J, K, M and N groups and the contribution from each of these groups therefore appears to merit some consideration.

Consanguinity in the parents of children with neural tube defects (B1-B7)

Consideration of the data in Table 19.5 shows that much the largest contribution to the number of related parents who had a child with a neural tube defect comes from Alexandria. In that centre the frequencies of all neural tube defects in children of parents of the different types were, first cousins and closer, 30/2109 (14.2 per 1000); related in less degree than first cousins, 9/1046 (8.6 per 1000); and unrelated 37/6431 (5.7 per 1000). This pattern strongly suggests a real influence of consanguinity.

As can be calculated from the figures, even if the Alexandria data are omitted there is still a significantly higher frequency in the other centres in the offspring of consanguineous marriages ($P > 0.001$). The other major contributing centre is Bombay. If the data from that centre are also removed there still remains an excess of consanguinity in remaining related parents of children with neural tube defects relative to those unrelated. However, after both the Bombay and Alexandria data have been removed the difference is no longer technically significant.

If we ignore neural tube defects there remain 3816 malformed children and, of these, 162 (4.2%) had consanguineous parents. The frequency of these malformations in the offspring of consanguineous marriages was 162/13 925 (11.6 per 1000) and their frequency in the offspring of unrelated marriages was 3816/352 866 (10.8 per 1000), a difference which is not significant.

It is clear, therefore, that in these data by far the most important contribution to any association between malformations and consanguinity is from the neural tube defects and further, that the two centres mainly contributing are Alexandria and Bombay. This is rather unexpected and a significant increase in the offspring having neural tube defects born to related parents has not been shown in any other data. However, in the only large series of cases where consanguinity of parents has been known to have been analysed, either the frequency of neural tube defects or that of consanguinity of parents has been low so that the data have not been very informative (Schull & Neel, 1965).

Polman (1951) and Penrose (1957) have suggested that some cases of anencephalus are determined by single recessive genes but the evidence has not been very impressive. It is not uncommon for women to give birth to two or more anencephalics in different pregnancies but this is usually attributed to unfavourable intra-uterine environmental influences and to support a predominantly maternal determination there is the well-known case of a woman who, having had three anencephalic foetuses by her husband, subsequently had a fourth following artificial insemination by donor (Horne, 1957). No morphological differences have been demonstrated in cases suspected of being determined by single recessive genes, although from other experience it would be expected that a difference would be detectable between a single-gene manifestation and a "phenocopy". These and other considerations mentioned in section 4, particularly the high correlations between countries of frequencies of neural tube defects, suggest that any single-gene contribution, if present, must be very small and contribute very little to the association between neural tube and consanguinity frequencies in the present data.

Harelip (G1) and harelip and cleft palate (G2)

Seven of 118 (5.5%) infants with harelip had related parents. In addition, of 10 cases where harelip was only one of two or more malformations, one was in the child of a consanguineous marriage.

In 13 of the 250 cases of harelip and cleft palate (5.2%) the parents were related, and in the 43 cases where harelip and cleft palate was one of other malformations and consanguinity was recorded, the parents of three were related.

These proportions are not significantly higher than in the parents of children who were not malformed. Little more can be said except that the findings by Schull (1958) in Japanese children were similar.

Cleft palate (G3) and consanguinity of parents

Of 83 cases of cleft palate the parents of six (7.4%) were related. There were also 34 cases of cleft palate in the N group and three were born to related parents. Taking cases in the G3 and N groups together, of the 117 cases nine had related parents.

It is difficult to interpret these data. In the Japanese data reported by Schull (1958), six of 35 cases of cleft palate had related parents but it is not clear from the data whether these included cases with other malformations. From time to time a small non-significant association of cleft palate and consanguinity has been reported in other series. It has now occurred so often that the association must be suspected of being real.

Malformations of the limbs and extremities (J) and consanguinity

There were 44 cases in the J group where the parents were related. The frequency of consanguinity in the parents in all affected in this group is significantly higher than in those of normal children ($P > 0.001$). However, cases appear to be scattered more or less at random over the seven subdivisions of the J group, and there are no significant differences in any one centre. As ulnar polydactyly and polydactyly (NFS) (which is mainly ulnar) predominate, inevitably most cases are in these subgroups. It must be suspected that some of the cases of polydactyly were part of a recessive gene syndrome not fully manifest or recognized at birth (e.g., ulnar polydactyly and juvenile cataract) or represented the only detectable malformation of several, the others being internal (as in many cases illustrated in the N group in the various centres; see the Basic Tabulations by Centres booklet).

Other local and general skeletal malformations (K) and consanguinity

There were five cases in this group where the parents were related and no more than one occurred in any centre. Two of the cases were of Pierre Robin syndrome, which might reasonably be assumed to be due to a single recessive gene. There were in all only 21 cases of this syndrome (including one in the N group).

Two other cases with related parents were of osteogenesis imperfecta. It is possible but unlikely that these also were due to single recessive genes. There were only 11 cases in all of this condition. However, cases of the severe type of this condition, which determines the " bag of bones " at birth, may have sibs with very mild manifestations, such as blue sclera only; and there is no reason to doubt from the recent work of Smårs (1961) that all types of cases are determined by single dominant genes. Of the remaining two cases in the K group with consanguineous parents one was of chondrodystrophy. As the child was stillborn and there is no evidence, such as the occurrence of chondrodystrophia foetalis in more than one sib, that the condition is ever caused by a recessive gene, nothing useful can be said.

The remaining case was of arthrogryphosis multiplex, which has only twice been recorded as occurring in sibs of an index case.

Consanguinity in parents of children with defects in the M group or miscellaneous group

There can be little doubt that the rather high proportion of consanguineous parents of children affected by one of these miscellaneous malformations is the result of the considerable number of single recessive gene traits in the group as discussed in section 15. Included in the 12 such cases listed in Table 19.6 are three cases of the anophthalmia/microphthalmia complex, which appears usually to be so determined; one case of epidermolysis bullosa in a child who died in hospital was almost certainly so caused, although non-lethal epidermolysis bullosa of the dominant type may be detectable at birth (Davison, 1965). " Agenesis of sclera " was reported in another child. It is difficult to know the meaning of this term, but the condition may have been due to a recessive gene.

Consanguinity in parents of children with multiple defects (N)

The defects in this group where parents were related are listed in Table 19.7. The frequency of multiple malformations is not significantly greater in the offspring of related than in those of unrelated parents. They are a varied group and on the whole

fairly representative in type of those in the rest of the N group. None of them appears to correspond to any syndrome generally accepted as being due to homozygosity for a single recessive gene and it is a matter of speculation as to whether any was so caused. As will be clear from the table, most of the cases occurred in centres where consanguinity rates are high. (Two cases from Mexico 2 are listed in this table, which accounts for the difference between the 19 cases listed and the 17 cases in the N group shown as having consanguineous parents in Table 19.5.)

DISCUSSION

As already stressed, the great majority of cases contributing to the increased frequency of malformation in the offspring of consanguineous parents were cases of neural tube defects, with anencephalus without spina bifida (B1) and with that defect (B2), spina bifida (B6), and hydrocephalus without spina bifida (B3) contributing most. There is a small but non-significant excess of other types of malformed children born to related parents but most, and indeed possibly all, of this excess is attributable to single recessive genes.

It is difficult to conceive of any substantial contribution to the neural tube defects being due to recessive genes, and the association with parental consanguinity of all types of anencephalus and hydrocephalus, taken together with the high correlations of the frequencies of these conditions in centres (section 4), suggest the need for a more complex explanation. The evidence for an effect of consanguinity on the frequency of stillbirth and death in the first few days of life considered above is rather convincing. The excess mortality in the offspring of related parents is reasonably uniformly distributed over all the centres when allowance is made for sampling fluctuations in centres where the frequency of consanguinity was low. Further, there is reassuring evidence from the significant differences in all comparisons between mortality in offspring of unrelated couples and those related in varying degrees.

Although the writers are not sufficiently convinced of the theoretical basis for making more elaborate calculations based on the mortality data, and have called attention to some of the uncertainties of the data, they would like to mention that in their opinion the data are much better than many which *have* been used for such calculations.

There has been much argument as to the interpretation of these associations of consanguinity with developmental anomalies. They are difficult to attribute to homozygosity for specific recessive genes and the general pattern is that, although they are found in sibs, parents or children, they so occur in frequencies which are too low for such monomeric interpretation, unless it is postulated that the genotype is only expressed as an abnormal phenotype in a small proportion of cases. Nevertheless the frequency in sibs is found to be perhaps 5-10 times as high as that in the general population. Although it is difficult to conceive of much failure of expression of harmful recessive genes in man it must be remembered that such an opinion is based to some extent on a circular argument, in that our only means of identifying such genes in man are segregation in the predicted Mendelian ratios in association with consanguinity. It is further extremely difficult to exclude in sibs uterine environmental factors in common rather than genotypic identity or similarity as the main determining factor.

It should be remembered that evidence previously advanced for a real association of consanguinity with the non-monofactorial types of developmental anomalies that constitute most of the malformations reported in this study is not at all strong. The question of such an association was raised by Neel & Schull (1956). Their findings appeared to suggest some slight association not technically significant over a range of malformations, perhaps in particular with children who had multiple malformations in uncommonly recurring patterns. They inclined to the view that these were unlikely to be due to homozygosity for very rare recessive genes which determine syndromes not generally recognized or studied. The numbers of neural tube defects in the Japanese data were small and perhaps did not constitute a sufficient basis on which to interpret associations with consanguinity, but there was, in fact, an increase of consanguinity in the parents of affected children.

Schull & Neel (1965) have recently considered the arguments concerning any associations of these morphological developmental failures with consanguinity of parents.

They may be summarized, as non-technically as possible, as follows:

(1) A large number of these conditions are predominantly the expression of single-gene mutations and their frequencies represent the relationships of gene frequencies, degrees of dominance and frequency of manifestation of the genotypes.

(2) Heterozygosity is necessary at a minimum number or proportion of gene loci if normal development is to take place. Inevitably even the contribution to reduction of heterozygosity from inbreeding in man, which is small relative to that from the intense inbreeding which can be practised in experimental animals, is reflected in a small increase in consanguinity of the parents of children with some of these anomalies. This is a gross over-simplification of some suggestions of Lerner (1954).

(3) The genotypic background to such developmental failures is predominantly multifactorial in the sense that it is a composite of the situation at many gene loci and that there is a substantial contribution of genes whose effects are essentially additive, i.e., without dominance or recesssiveness. On such a hypothesis normal development is probably up to a certain level of accumulation of plus or minus values or combinations of such genes, but beyond that threshold normal development becomes increasingly less likely ; the effective value for the threshold is probably varied considerably by environmental factors.

There is a tendency in all such discussions to forget how heterogeneous many of these traits really are and that for purposes of numerical analysis anomalies are often grouped together which are really only similar, not identical, because discrimination of the morbid anatomy has not yet served to make adequate separations. As a result, the cases may well be a mixture of cases determined at single-gene loci, cases determined by more complex mechanisms and cases where the genotypic contribution is minimal or absent.

In essence, none of these hypotheses is easy to prove or disprove, at least to the satisfaction of all geneticists, and it seems likely that all are valid in different cases. It is hoped that, as a result of this study, some more detailed investigation designed to elucidate some of these problems will be undertaken. There are some suggestions along these lines in section 21.

TABLE 19.1

CONSANGUINITY AND SURVIVAL OF SINGLE-BORN INFANTS NOT MALFORMED [a]

CENTRE		LBA							LBD + SB						
		Consanguinity of parents				% of LBA whose parents were:			Consanguinity of parents				% of LBD + SB whose parents were:		
		FC & CFC	LFC	None	Total	FC & CFC	LFC	In any way related	FC & CFC	LFC	None	Total	FC & CFC	LFC	In any way related
I 1	MELBOURNE	26	11	7377	7414	0.35	0.15	0.50	2	0	277	279	0.72	0.00	0.72
I 2	MELBOURNE	21	26	3711	3758	0.56	0.69	1.25	0	1	84	85	0.00	1.19	1.18
II	SAO PAULO	255	166	13160	13581	1.88	1.22	3.10	12	4	582	598	2.00	0.67	2.67
III	SANTIAGO	170	8	22247	22425	0.76	0.03	0.79	10	0	1056	1066	0.94	0.00	0.94
IV 1	BOGOTA	129	237	17418	17774	0.72	1.28	2.00	7	11	705	723	0.97	1.52	2.49
IV 2	MEDELLIN	609	259	18774	19642	3.10	1.32	4.42	13	9	482	504	2.58	1.78	4.36
V	CZECHOSLOVAKIA	9	21	19355	19385	0.05	0.10	0.15	0	0	341	341	0.00	0.00	0.00
VI	ALEXANDRIA	1892	962	5855	8709	21.72	11.05	32.78	180	73	514	767	23.47	9.52	32.98
VII	HONG KONG	148	25	9390	9563	1.55	0.26	1.81	0	0	186	186	0.00	0.00	0.00
VIII 1	BOMBAY	3117	370	32947	36434	8.55	1.02	9.57	310	26	2385	2721	11.39	0.96	12.35
VIII 2	CALCUTTA	85	0	17923	18008	0.47	0.00	0.47	8	0	1102	1110	0.73	0.00	0.73
IX 1	KUALA LUMPUR	814	296	13809	14919	5.46	1.98	7.44	62	19	658	739	8.39	2.57	10.96
IX 2	SINGAPORE	1496	424	36778	38698	3.87	1.09	4.96	48	9	578	635	7.56	1.42	8.98
X 1	MEXICO CITY	64	16	23668	23748	0.27	0.07	0.34	2	0	583	585	0.34	0.00	0.34
X 2	MEXICO CITY														
XI	BELFAST														
XII	PANAMA CITY	228	30	14930	15188	1.50	0.20	1.70	9	1	325	335	2.68	0.30	2.98
XIII	MANILA	82	33	28319	28434	0.29	0.11	0.40	1	4	974	979	0.10	0.41	0.51
XIV 1	CAPE TOWN	21	0	2809	2830	0.74	0.00	0.74	1	0	183	184	0.54	0.00	0.54
XIV 2	JOHANNESBURG	28	9	10528	10565	0.26	0.08	0.35	5	0	339	344	1.45	0.00	1.45
XIV 3	PRETORIA	493	81	8886	9460	5.21	0.86	6.07	20	1	350	371	5.39	0.28	5.66
XV	MADRID	96	106	18431	18633	0.51	0.57	1.08	2	2	728	732	0.27	0.27	0.55
XVI 1	LJUBLJANA	15	33	8485	8533	0.18	0.38	0.56	0	3	176	179	0.00	1.67	1.67
XVI 2	ZAGREB	2	5	8131	8138	0.02	0.06	0.08	0	0	171	171	0.00	0.00	0.00
	TOTAL	9800	3108	342931	355838	2.75	0.88	3.63	692	163	12779	13634	5.07	1.20	6.27

[a] Births where consanguinity was not recorded are excluded.

TABLE 19.2

COMPARISON OF FREQUENCY IN OFFSPRING OF RELATED AND UNRELATED PARENTS OF (A) STILLBIRTH OR DEATH IN HOSPITAL BUT NOT MALFORMATION AND (B) MALFORMATION

CENTRE		A LBD + SB (Malformed excluded)					Ratio Obs./ Exp.	Significance of difference between Observed & Expected[a]	B All malformed					Ratio Obs./ Exp.	Significance of difference between Observed & Expected[a]
		Not related		Related					Not related		Related				
		Total births	SB + LBD	Total births	SB + LBD Obs.	SB + LBD Exp.			Total births	Malf.	Total births	Malf. Obs.	Malf. Exp.		
I 1	MELBOURNE	7654	277	39	2	1.41	1.42	NS	7801	147	40	1	0.75	1.33	NS
I 2	MELBOURNE	3795	84	48	1	1.06	0.94	NS	3862	67	49	1	0.85	1.18	NS
II	SAO PAULO	13742	582	437	16	18.51	0.86	NS	13963	221	447	10	7.07	1.41	NS
III	SANTIAGO	23303	1056	188	10	8.52	1.17	NS	23522	219	193	5	1.80	2.78	NS
IV 1	BOGOTA	18123	705	374	18	14.55	1.24	NS	18424	301	388	14	6.34	2.21	+
IV 2	MEDELLIN	19256	482	890	22	22.28	0.99	NS	19462	206	911	21	9.64	2.18	++
V	CZECHOSLOVAKIA	19696	341	30	-	0.52	-	NS	20040	344	34	4	0.58	6.90	++
VI	ALEXANDRIA	6369	514	3107	253	250.75	1.01	NS	6431	63	3155	48	30.91	1.55	++
VII	HONG KONG	9576	186	173	-	3.36	-	*	9686	110	177	4	2.01	1.99	NS
VIII 1	BOMBAY	35332	2385	3823	336	258.06	1.30	++	35620	288	3875	52	31.33	1.66	++
VIII 2	CALCUTTA	19025	1102	93	8	5.39	1.48	NS	19084	59	93	-	0.29	-	NS
IX 1	KUALA LUMPUR	14467	658	1191	81	54.17	1.50	++	14621	154	1204	13	12.68	1.03	NS
IX 2	SINGAPORE	37356	578	1977	57	30.59	1.86	++	37674	318	2002	25	16.90	1.48	NS
X 1	MEXICO CITY	24251	583	82	2	1.97	1.02	NS	24611	360	86	4	1.26	3.17	NS
X 2	MEXICO CITY														
XI	BELFAST														
XII	PANAMA CITY	15255	325	268	10	5.71	1.75	NS	15571	316	281	13	5.70	2.28	++
XIII	MANILA	29293	974	120	5	3.99	1.25	NS	29542	249	123	3	1.04	2.88	NS
XIV 1	CAPE TOWN	2992	183	22	1	1.35	0.74	NS	3018	36	22	-	0.26	-	NS
XIV 2	JOHANNESBURG	10867	339	42	5	1.31	3.82	+	1117	250	44	2	9.85	0.20	[b]
XIV 3	PRETORIA	9236	350	595	21	22.55	0.93	NS	9354	118	606	11	7.64	1.44	NS
XV	MADRID	19159	728	206	4	7.83	0.51	NS	19418	259	211	5	2.81	1.78	NS
XVI 1	LJUBLJANA	8661	176	51	3	1.04	2.89	NS	8827	170	52	1	1.00	1.00	NS
XVI 2	ZAGREB	8302	171	7	-	0.14	-	NS	8409	107	7	-	0.09	-	NS
	TOTAL	355710	12779	13763	855	494.44	1.73	$\chi^2 = 262.2$	360057	4352	14000	237	169.22	1.40	$\chi^2 = 26.75$

[a] NS = not significant; + or ++ = significant at 5 % or 1 % level (Poisson); * = significant at 5 % level (exact χ^2 test).

[b] Fewer cases among related parents significant at 1 % level.

TABLE 19.3

MORTALITY IN SINGLE BIRTHS [a] BY SEX IN THE DIFFERENT TYPES OF FIRST-COUSIN MARRIAGES

Centre	Consanguinity code [b]												All other [b] (consanguinity codes 1, 6, 7, 8, 9, and 0)					
	3				5				2 + 4									
	M		F		M		F		M		F		M		F		T	
	LBD + SB	T	LBD + SB	T	LBD + SB	T	LBD + SB	T	LBD + SB	T	LBD + SB	T	LBD + SB	T	LBD + SB	T	LBD + SB	T
São Paulo	0	30	2	39	1	23	1	27	5	67	3	54	349	7154	235	6782	584	13936
Bombay	7	85	9	80	48	618	45	559	104	1011	89	907	1321	18815	1098	17080	2419	35895
Kuala Lumpur	2	42	4	47	9	112	4	99	11	150	7	149	343	7765	357	7274	700	15039
Singapore	11	164	—	153	4	213	4	176	12	268	10	245	313	19713	279	18398	592	38111
Pretoria	—	33	3	42	3	49	3	58	5	171	5	158	187	4747	166	4565	353	9312

[a] Excluding children with malformations and those whose sex was not recorded or indeterminate.

[b] Consanguinity coding is explained in Annex 2 under the blank form for Table IX used in the Basic Tabulations by Centres booklet.

TABLE 19.4

CONSANGUINITY AND MAJOR MALFORMATIONS IN SINGLE BIRTHS [a]

CENTRE		ALL NOT MALFORMED							ALL MALFORMED						
		Consanguinity of parents				% of not malformed whose parents were:			Consanguinity of parents				% of malformed whose parents were:		
		FC & CFC	LFC	None	Total	FC & CFC	LFC	In any way related	FC & CFC	LFC	None	Total	FC & CFC	LFC	In any way related
I 1	MELBOURNE	28	11	7654	7693	0.36	0.14	0.50	1	0	147	148	0.67	0.00	0.67
I 2	MELBOURNE	21	27	3795	3843	0.54	0.67	1.22	0	1	67	68	0.00	1.47	1.47
II	SAO PAULO	267	170	13742	14179	1.88	1.20	3.08	5	5	221	231	2.16	2.16	4.32
III	SANTIAGO	180	8	23303	23491	0.77	0.03	0.80	5	0	219	224	2.23	0.00	2.23
IV 1	BOGOTA	136	238	18123	18497	0.73	1.29	2.02	7	7	301	315	2.22	2.22	4.44
IV 2	MEDELLIN	622	268	19256	20146	3.09	1.33	4.42	15	6	206	227	6.61	2.64	9.25
V	CZECHOSLOVAKIA	9	21	19696	19726	0.04	0.11	0.15	1	3	344	348	0.29	0.86	1.15
VI	ALEXANDRIA	2072	1035	6368	9475	21.87	10.92	32.79	37	11	63	111	33.33	10.00	43.24
VII	HONG KONG	148	25	9576	9749	1.52	0.25	1.77	2	2	110	114	1.75	1.75	3.50
VIII 1	BOMBAY	3427	396	35332	39155	8.75	1.01	9.76	51	1	288	340	15.00	0.29	15.29
VIII 2	CALCUTTA	93	0	19025	19118	0.49	0.00	0.49	0	0	59	59	0.00	0.00	0.00
IX 1	KUALA LUMPUR	876	315	14467	15658	5.59	2.01	7.60	8	5	154	167	4.79	2.99	7.78
IX 2	SINGAPORE	1544	433	37356	39333	3.92	1.10	5.02	17	8	318	343	4.96	2.33	7.29
X 1	MEXICO CITY	66	16	24251	24333	0.27	0.07	0.34	2	2	360	364	0.55	0.55	1.10
X 2	MEXICO CITY														
XI	BELFAST														
XII	PANAMA CITY	237	31	15255	15523	1.53	0.20	1.73	10	3	316	329	3.04	0.91	3.95
XIII	MANILA	83	37	29293	29413	0.28	0.13	0.41	1	2	249	252	0.40	0.79	1.19
XIV 1	CAPE TOWN	22	0	2992	3014	0.73	0.00	0.73	0	0	26	26	0.00	0.00	0.00
XIV 2	JOHANNESBURG	33	9	10867	10909	0.30	0.08	0.38	2	0	250	252	0.79	0.00	0.79
XIV 3	PRETORIA	513	82	9236	9831	5.22	0.83	6.05	11	0	118	129	8.53	0.00	8.53
XV	MADRID	98	108	19159	19365	0.50	0.56	1.06	4	1	259	264	1.51	0.38	1.89
XVI 1	LJUBLJANA	15	36	8661	8712	0.17	0.41	0.58	1	0	170	171	0.60	0.00	0.60
XVI 2	ZAGREB	2	5	8302	8309	0.02	0.06	0.08	0	0	107	107	0.00	0.00	0.00
	TOTAL	10492	3271	355709	369472	2.84	0.88	3.72	180	57	4352	4589	3.92	1.24	5.17

[a] Births where consanguinity was not recorded are excluded.

TABLE 19.5

MALFORMATIONS BY GROUPS IN SINGLE BIRTHS: NUMBERS AND PROPORTIONS WHERE PARENTS WERE RELATED AND CONSANGUINITY WAS RECORDED

CENTRE	NUMBERS WHERE PARENTS WERE RELATED IN ANY DEGREE / NUMBERS OF ALL MALFORMED																		
	A	B 1 & 2	B 3	B 4	B 5 & 7	B 6	C	D	E	F	G 1 & 2	G 3	H	I	J	K	L	M	N	Total
I 1 MELBOURNE	0/8	0/8	0/12	0/2	0/3	0/3	0/2	0/12	0/9	0/2	0/10	0/1	0/26	0/7	0/13	0/3	0/6	0/8	1/13	1
I 2 MELBOURNE	0/6	0/2	0/3	0/4	0/0	0/3	0/0	0/6	0/6	0/0	0/0	0/2	0/10	0/0	0/6	0/1	0/0	1/11	0/8	1
II SAO PAULO	1/11	0/9	1/13	0/2	0/2	0/14	0/2	0/9	0/14	0/3	2/14	0/5	1/43	0/0	2/65	1/4	0/10	0/3	2/8	10
III SANTIAGO	2/37	0/7	1/8	0/1	0/3	0/10	0/1	0/3	0/6	0/0	0/27	0/6	1/48	0/9	1/30	0/6	0/6	0/9	0/7	5
IV 1 BOGOTA	0/10	0/2	1/16	0/1	0/2	0/1	0/0	0/9	0/6	0/0	3/24	0/3	3/99	1/61	5/48	0/6	0/5	0/9	1/13	14
IV 2 MEDELLIN	2/17	0/6	0/7	0/0	0/0	1/4	0/0	1/17	0/3	0/0	4/27	0/0	4/51	0/4	4/55	1/4	0/3	1/8	3/21	21
V CZECHOSLOVAKIA	1/27	1/11	0/7	0/5	0/3	0/12	1/13	0/34	0/23	0/7	1/12	0/10	0/69	0/0	0/38	0/17	0/11	0/18	0/31	4
VI ALEXANDRIA	0/0	19/36	9/20	4/6	2/6	5/8	0/0	1/1	0/4	0/0	2/9	0/0	0/5	0/0	1/5	1/2	0/0	2/4	2/5	48
VII HONG KONG	0/1	1/13	0/4	0/1	0/1	0/3	0/0	0/9	0/5	0/0	0/14	0/2	0/16	0/0	3/19	0/5	0/2	0/4	0/15	4
VIII 1 BOMBAY	0/0	6/66	4/30	5/12	0/4	2/30	0/1	2/9	4/23	0/1	4/43	2/5	4/38	0/0	11/34	1/6	1/6	3/10	3/22	52
VIII 2 CALCUTTA	0/0	0/7	0/1	0/0	0/1	0/2	0/0	0/2	0/3	0/0	0/12	0/3	0/8	0/0	0/14	0/0	0/4	0/2	0/0	0
IX 1 KUALA LUMPUR	0/3	2/18	1/16	0/0	0/0	0/3	0/1	0/4	1/15	0/1	1/25	0/0	3/26	0/1	2/21	0/3	0/3	3/19	0/8	13
IX 2 SINGAPORE	2/17	3/28	0/9	0/0	0/1	1/5	0/2	0/0	0/9	1/3	2/56	3/13	8/116	0/0	3/61	0/0	0/0	1/7	1/16	25
X 1 MEXICO CITY	1/46	0/29	0/12	0/5	0/4	1/16	0/2	0/18	0/19	0/4	0/20	0/3	0/70	0/1	0/46	1/12	0/7	0/14	1/36	4
XII PANAMA CITY	0/17	1/9	3/15	0/2	0/1	0/10	0/1	0/2	0/2	0/4	0/11	0/0	5/172	0/3	4/57	0/5	0/2	0/4	0/12	13
XIII MANILA	1/17	0/15	0/8	0/1	0/5	0/1	0/1	0/21	0/10	0/4	0/33	0/12	0/27	0/0	0/43	0/5	0/5	0/13	2/31	3
XIV 1 CAPE TOWN	0/0	0/2	0/2	0/0	0/1	0/2	0/0	0/3	0/1	0/0	0/0	0/1	0/2	0/0	0/5	0/1	0/1	0/2	0/3	0
XIV 2 JOHANNESBURG	0/8	0/9	0/6	0/1	0/1	0/9	0/0	1/26	1/13	0/8	0/18	0/1	0/77	0/0	0/31	0/9	0/9	0/7	0/19	2
XIV 3 PRETORIA	0/6	0/5	0/11	1/5	0/0	0/6	0/0	0/2	1/4	0/0	0/1	1/4	1/12	0/0	6/62	0/1	0/2	1/4	0/4	11
XV MADRID	0/39	0/16	0/7	0/4	0/0	0/8	0/0	0/65	0/9	0/5	1/13	0/7	1/37	0/0	2/26	0/3	0/7	0/7	1/11	5
XVI 1 LJUBLJANA	0/20	0/1	0/5	0/5	0/1	0/3	0/4	0/9	0/3	0/2	0/5	0/3	1/42	0/27	0/8	0/10	0/2	0/11	0/10	1
XVI 2 ZAGREB	0/6	0/5	0/4	0/1	0/0	0/3	0/0	0/6	0/7	0/0	0/4	0/2	0/35	0/0	0/14	0/4	0/5	0/4	0/7	0
TOTAL CONSANGUINITY	10	33	20	10	2	10	1	5	7	1	20	6	32	1	44	5	1	12	17	237
TOTAL MALFORMATIONS	296	304	216	58	39	156	30	267	194	44	378	83	1029	113	701	107	96	178	300	4589
CONSANGUINITY (%)	3.3	10.8	9.2	19.8	5.1	6.4	3.3	1.9	3.6	2.3	5.3	7.2	3.1	0.9	6.3	4.7	1.0	6.7	5.7	5.2

TABLE 19.6 MALFORMATIONS IN SINGLE-BORN INFANTS IN M GROUP WHOSE PARENTS WERE RELATED

Centre	No. in M group	Sex and survival	Consanguinity	Malformations
Melbourne 2	M 10	F LBD	LFC	Epidermolysis bullosa
Medellín	M 2	F LBA	LFC	Epigastric hernia
Alexandria	M 1	M SB	FC	Absence of bridge of nose; microphthalmia
Alexandria	M 2	F SB	LFC	Failure of midline fusion of mandible
Bombay	M 2	F LBA	FC	Anophthalmia
Bombay	M 3	M LBA	FC	Anophthalmia
Bombay	M 4	M LBD	FC	" Agenesis of sclera "
Kuala Lumpur	M 10	M LBD	LFC	" Conjunctival opacities " (? corneal)
Kuala Lumpur	M 12	M SB	FC	Marfan's syndrome
Kuala Lumpur	M 18	F SB	FC	" Monster "
Singapore	M 4	F LBA	LFC	Anophthalmia
Pretoria	M 2	M SB	FC	Massive thyroid tumour

TABLE 19. 7 MALFORMATIONS IN SINGLE-BORN INFANTS IN N GROUP WHOSE PARENTS WERE RELATED

Centre	No. in N group	Sex and survival	Consan-guinity	Malformations
Melbourne 1	N 8	M LBA	LFC	Tracheo-oesophageal fistula; imperforate anus; absent radii
São Paulo	N 4	M LBA	LFC	Cleft nose; recurved penis
São Paulo	N 7	? LBD	FC	Indeterminate sex; horseshoe kidney; open cranial suture
Bogotá	N 3	M LBD	FC	Agenesis of nose; hypoplasia of penis; talipes; agenesis of 2nd phalanges of fingers 2, 3 and 4
Medellín	N 9	M LBA	FC	HL/CP; polydactyly (ulnar); cranium bifidum
Medellín	N 12	? SB	FC	HL; exomphalos; ambiguous genitalia
Medellín	N 20	F SB	FC	" Absence " of neck; aplasia of genitalia
Alexandria	N 1	M LBA	FC	Talipes; abnormal features
Alexandria	N 3	M SB	FC	Talipes; ankylosis of knees; clubbed hands; hypospadias
Bombay	N 4	M LBA	FC	HL/CP; imperforate anus
Bombay	N 8	M LBD	CFC	HL/CP; polydactyly (ulnar); talipes
Bombay	N 11	M LBA	FC	CP; talipes
Singapore	N 4	F LBA	LFC	CP; atresia of auditory meatus
Mexico 1	N 10	F LBD	FC	Fissure of gum; short limbs; defects of digits of hands and feet
Mexico 2	N 7	M LBA	LFC	Talipes; low-set ears
Mexico 2	N 11	M LBA	LFC	CP; micrognathia; abnormal position of ear
Manila	N 7	M LBA	LFC	HL/CP; shield-like chest and hypoplastic breasts
Manila	N 20	F LBD	LFC	Anophthalmia; microtia; microstomia; micromelia; rudimentary digits
Madrid	N 4	M LBA	LFC	Arthrogryphosis multiplex; hypospadias